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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,395	08/18/1999	LEAF HUANG	226272002201	6461
25226	7590	12/19/2003		
MORRISON & FOERSTER LLP 755 PAGE MILL RD PALO ALTO, CA 94304-1018			EXAMINER SCHNIZER, RICHARD A	
			ART UNIT 1635	PAPER NUMBER

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/376,395	HUANG ET AL.	
Examiner	Art Unit	
Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 26 August 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 77,80,81,83-86,88-95,97-101,103-123,125-131 and 133-177 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 77,80,81,83-86,88-95,97-101,103-123,125-131 and 133-177 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 May 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 5) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

An amendment was received and entered on 8/26/03.

Claims 78, 79, and 82 were canceled and claims 156-177 were added as requested.

Claims 77, 80, 81, 83-86, 88-95, 97-101, 103-123, 125-131, and 133-177 are pending and under consideration in this Office Action.

The invention as originally filed was drawn to drug compositions and methods of making and using them. In response to a restriction requirement, Applicant elected in Paper No. 10 group III drawn to therapeutic compositions comprising nucleic acids and methods of making and using them. Applicant also elected asialoglycoprotein as the species of targeting ligand to be examined. The species was deemed to read on all the claims. In the previous Office Action it was indicated that claims 88 and 125 were novel and non-obvious to the extent that they read on the species of invention comprising asialoglycoprotein, but the claims as generically written were obvious. After further consideration, the restriction requirement among the species of targeting ligand is withdrawn, as a review of the prior art indicates that such ligands are routinely substituted for one another. As such, and in view of the new grounds of rejection set forth below, the indication of novelty and non-obviousness of claims 88 and 125 is withdrawn. Furthermore, it was previously indicated that claims 81-83, 111 and 112 would be allowable if rewritten as independent claims incorporating all of the limitations of the claims from which they depend. This indication is withdrawn in view of the new grounds of rejection set forth below.

Priority

The instant Application claims priority to two US Patents (5,795,587, filed 1,23/95; and 6,008,202, filed 9/29/97) and to abandoned application serial number 08/751,888, filed 11/18/96. Currently the application contains two claims (88 and 125), reciting compositions comprising an E1A gene. However, this embodiment finds no support in two of the three priority documents, US 5,795,587 and abandoned application serial number 08/939,874. For these reasons the effective filing date of claims 88 and 125 is 9/29/97. Similarly, support for shielding or PEG-modification of complexes is found only in US Patent 6,008,202, and not in the other two priority documents. So the priority date for claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154, and 155 is 9/29/97.

Drawings

The drawings stand objected to for the reasons of record in the Action mailed 3/15/01.

Rejections Withdrawn

After further consideration, rejection of claims 113-123, 125-131, and 133-153 are rejected under 35 U.S.C. 112, first paragraph is withdrawn.

Claim Objections

Claim 114 is objected to because "intravenously" is misspelled.

Claim 169 is objected to because it fails to further limit claim 156 which already requires that the complex has a diameter of less than about 400 nm.

Claims 99 and 34 are objected to as lacking a comma after the word "lipid".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 77, 89-94, 98-101, 104, 107-109, 139-141, 144-150, 156, 164-169, and 172-177 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,795,587 in view of Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992).

The claims of '587 are drawn to methods of making non-covalent nucleic acid/lipid/polycationic polypeptide complexes with a net positive charge at about pH 6-8. The ratio of lipid to nucleic acid may be 0.1 nmol-200nmol lipid per 1 microgram of nucleic acid. See claim 2. The ratio of polycation to nucleic acid is about 0.01 -100

microgram polycation to 1 microgram nucleic acid. See claim 4. The polycation may be poly-L-lysine of between 300 and 200,000 Daltons. See claim 6. The complexes may comprise cationic liposomes comprising DC-Chol and neutral phospholipids, see claim 6. The complex may have a diameter of less than 400 nm. See claim 7. Also claimed are the compositions themselves (claims 8-14 and 21), and methods of using them to deliver nucleic acids to cells (claims 15-20).

The claims of '587 are silent as to whether or not the polycationic polypeptides are salts, and do not recite any targeting factor. The specification of '587 teaches that polylysine (MW = 3,000 and MW= 25,600) was obtained from Sigma. See column 11, lines 60-62.

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine/gene complexes improves transfection efficiency. The polylysine of Mack was MW=39,400, purchased from Sigma (Sigma catalog indicates that this preparation is a salt). See sentence bridging pages 138 and 139.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add a targeting ligand to the methods and compositions of '587 because Mack teaches that use of a targeting ligand allows delivery to specific cells that comprise a receptor for the ligand. See paragraph bridging columns 1 and 2 on page 138, and first and third full paragraphs of column 2 on page 142.

Claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, and 9-11 of U.S. Patent No. 5,795,587, in view of Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992) and Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988).

Claim 6 of '587 teaches nucleic acid/lipid/polycationic polypeptide complex with a net positive charge, wherein the lipids include DC-Chol and a neutral colipid, and the polypeptide is polylysine with a molecular weight of between 300-200,000. This molecular weight range overlaps the range of polypeptide lengths recited in instant claim 128. Claim 7 of '587 requires that the size of the particles must be less than 400 nm. Claims 9-11 of '587 recite ratios of lipids, nucleic acids, and polycations, overlapping those required by instant claim 134.

Claims 6, 7, and 9-11 of '587 do not require deliver of the complexes to an individual.

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine/gene complexes improves transfection efficiency.

Wu teaches a method of intravenously delivering to cells of an individual *in vivo* DNA encoding a reporter gene (chloramphenicol acetyltransferase). Wu teaches the formation of complexes between the DNA and asialoglycoprotein-modified polylysine. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the complexes of '587 *in vivo*, because Mack teaches complexes having all of the characteristics of claims 113-117, 126, 128-130, 134 and 135, and Wu teaches that asialoglycoprotein-targeted nucleic acid particles should be delivered *in vivo*. In view of the results of Wu, one would have a reasonable expectation of success for *in vivo* delivery of these particles.

Claims 95, 97, 98, 107, 131, 133, 137, 138, 142, 143, 154, 155, 170, and 171 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, and 9-11 of U.S. Patent No. 5,795,587, Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992), and Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988) as applied to claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 above and further in view of Torchilin et al (FASEB J. 6(9): 2716-2719, 1992).

The teachings of '587, Wu, and Mack can be combined to render obvious methods of delivering nucleic acid/lipid/polycationic polypeptide salt complexes intravenously.

These references do not teach shielded complexes.

Torchilin teaches that PEG-modification of targeted liposomes is advantageous for intravenous delivery because it allows prolonged circulation and avoidance of rapid clearance. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to nucleic acid/lipid/polycationic polypeptide salt complexes by attachment of polyethylene glycol for intravenous delivery. One would have been motivated to do so because Torchilin teaches that this overcomes the problem of rapid particle clearance from the bloodstream, thereby increasing the chance of accurate targeting.

Thus the invention as a whole was prima facie obvious.

Claims 77, 88-94, 98-101, 104, 105, 107-109, 113, 115-117, 125, 126, 130, 134-136, and 151-153, 156, 163-169, and 172-177 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,795,587, in view of Trubetskoy et al (1992), Hung et al (US Patent

5,651,964, issued 7/29/97), and Kern et al (CANCER RESEARCH, (1990 Aug 15) 50 (16) 5184-7).

The claims of '587 are drawn to methods of making non-covalent nucleic acid/lipid/polycationic polypeptide complexes with a net positive charge at about pH 6-8. The ratio of lipid to nucleic acid may be 0.1 nmol-200 nmol lipid per 1 microgram of nucleic acid. See claim 2. The ratio of polycation to nucleic acid is about 0.01 -100 microgram polycation to 1 microgram nucleic acid. See claim 4. The polycation may be poly-L-lysine of between 300 and 200,000 Daltons. See claim 6. The complexes may comprise cationic liposomes comprising DC-Chol and neutral phospholipids, see claim 6. The complex may have a diameter of less than 400 nm. See claim 7. Also claimed are the compositions themselves (claims 8-14 and 21), and methods of using them to deliver nucleic acids to cells (claims 15-20).

The claims of '587 do not recite any targeting factor, methods of in vivo delivery, or use of an E1A gene.

Trubetskoy teaches of antibody-modified polylysine, plasmid DNA, and cationic liposomes, and methods of using the complexes to transfect mouse lung endothelial cells (see abstract).

Hung teaches methods of suppressing growth of a neu-oncogene-mediated tumor in a mammal by delivery to the tumor of a plasmid comprising a nucleic acid sequence encoding an adenoviral E1A gene product. See claim 2.

Kern teaches that neu is overexpressed in several types of lung cancer. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add a targeting ligand to the methods and compositions of '587 because Trubetskoy teaches that use of a targeting ligand allows delivery to specific cells that

comprise a receptor for the ligand. It would have been obvious to one of ordinary skill in the art at the time of the invention to use an E1A-encoding plasmid with the targeted polycationic polypeptide and liposomes of Trubetskoy for delivery to neu-oncogene-mediated lung tumors in mice. One would have been motivated to do so because Hung teaches that delivery of E1A genes to neu-oncogene mediated tumors suppresses the growth of the tumors. One would have been motivated to deliver the complexes to a lung tumor because Kern teaches that many lung tumors are characterized by overexpression of neu. One would have had a reasonable expectation of success because the targeting ligand of Trubetskoy mediated successful transfection of mouse lung cells in vitro.

Response to Arguments

Applicant's arguments filed 8/26/03 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant acknowledges that the cited art teaches polycationic polypeptides, but argues that the references (Mack and the '587 patent in particular) do not teach salts of the polycationic polypeptides. This is unpersuasive for the following reasons. The claims of '587 are silent as to whether or not the polycationic polypeptides are salts, but the specification of '587 teaches that poly-L-lysine (MW = 3,000 and MW= 25,600) was obtained from Sigma. See column 11, lines 60-62. The instant specification teaches that that poly-L-lysine hydrobromide (MW = 3,000 and MW= 25,600) was obtained from Sigma. Mack teaches that polylysine of MW=39,400 was purchased from Sigma. See sentence bridging pages 138 and 139. As evidenced by page 1745 of the 1992 Sigma Chemical Company catalog, Sigma offers poly-L-lysine in these molecular weight

ranges only as hydrobromide or hydrochloride salts. Absent evidence to the contrary, the polylysines of '587 and Mack are salts.

Claims 77, 80, 81, 83-86, 89-94, 98-101, 103, 104, 107-112, 139-141, 144-150, 156-162, 164-169, and 172-177 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,795,587, in view of Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992), and Birnstiel et al (US Patent 5,922,859, issued 7/13/99).

The '587 Patent and Mack can be combined to render obvious methods of making and using complexes non-covalent nucleic acid/lipid/polycationic polypeptide salt complexes with a net positive charge at about pH 6-8, as discussed above. In particular the '587 patent teaches the following. The ratio of lipid to nucleic acid may be 0.1 nmol-200nmol lipid per 1 microgram of nucleic acid. See claim 2. The ratio of polycation to nucleic acid is about 0.01 -100 microgram polycation to 1 microgram nucleic acid. See claim 4. The polycation may be poly-L-lysine of between 300 and 200,000 Daltons. See claim 6. The complexes may comprise cationic liposomes comprising DC-Chol and neutral phospholipids, see claim 6. The complex may have a diameter of less than 400 nm. See claim 7. Also claimed are the compositions themselves (claims 8-14 and 21), and methods of using them to deliver nucleic acids to cells (claims 15-20).

These references do not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor do they teach a sulfate salt, or protamine as a polycation.

Birnstiel teaches methods and compositions for delivering DNA to cells. The complexes comprise a polycationic polypeptide for condensing the DNA, as well as a targeting ligand. See e.g. claims 1, 14, and 17. Birnstiel also teaches that protamine and polylysine salts may be used interchangeably in such compositions. See column 18 line 66 to column 19, line 25. As evidenced by the instant specification at page 47 (Table 5) protamine sulfate meets the limitations of claim 81 with respect to the quantities of arginine and lysine required in the polypeptide salt.

Birnstiel teaches compositions for delivering nucleic acids to cells. The compositions comprise

- (a) the nucleic acid to be transferred;
- (b) an internalizing factor-bonding factor conjugate complexed to the nucleic acid to be transferred; and
- (c) a non-covalently bound substance having an affinity for nucleic acid, which substance is not a component of said internalizing factor-bonding factor conjugate; wherein
 - (i) said internalizing factor is cell type specific for said eukaryotic cells;
 - (ii) said non-covalently bound substance is selected from a group consisting of polycations that are capable of condensing the nucleic acid to be transferred, histones, and HMGI; and
 - (iii) the ability of said complex to internalize and/or achieve expression of said nucleic acid to be transferred is increased compared to the complex containing only the nucleic acid to be transferred and the internalizing factor-bonding factor conjugate.

Birnstiel exemplifies polylysine/transferrin conjugates as "internalizing factor-bonding factor conjugates", and exemplifies a variety of polycationic polypeptide salts

as "a non-covalently bound substance having an affinity for nucleic acid." Experiments characterizing these compositions were conducted. First Birnstiel studied compositions comprising only transferrin/polylysine conjugates complexed with DNA, and determined the optimum amount of conjugate per unit DNA. Then Birnstiel formed complexes between DNA and a suboptimal amount of transferrin/polylysine conjugate, and then added free polycationic polypeptide salts such as polylysine (55, 90, or 450 residues), protamine sulfate, or histone. Birnstiel found that "the addition of polylysines and natural protamine and the histones investigated achieved a DNA import efficiency at least equivalent to that obtained when using the conjugates which had been found to be optimum." See column 17, line 10 to column 19, line 25, especially column 18, line 47 to column 19, line 25, and Table 1 at column 27.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lipids of '587 to the compositions of Birnstiel because Mack teaches that the addition of cationic lipids to polycation/ligand/DNA complexes increases transfection efficiency more than 10-fold over that achieved in the absence of lipids, without the need for chloroquine. See paragraph bridging columns 1 and 2, and Fig. 3, on page 140. Thus one of ordinary skill in the art could reasonably have expected to increase the efficiency of transfection of the complexes of Birnstiel.

Claims 106 and 118-123 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, and 9-11 of U.S. Patent No. 5,795,587, in view of Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992) and Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988) as applied to claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 above and further in view of Birnstiel et al (US Patent 5,922,859, issued 7/13/99).

The teachings of the '587 patent, Mack, and Wu are described above and can be combined to render obvious methods of delivering in vivo complexes comprising nucleic acids, polycationic polypeptide salts and cationic lipids.

These references do not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor do they teach a sulfate salt, or protamine as a polycation. The teachings of Birnstiel are discussed above. Birnstiel teaches polylysine/transferrin/nucleic acid complexes comprising protamine sulfate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lipids of '587 to the compositions of Birnstiel because Mack teaches that the addition of cationic lipids to polycation/ligand/DNA complexes increases transfection efficiency more than 10-fold over that achieved in the absence of lipids, without the need for chloroquine. See paragraph bridging columns 1 and 2, and Fig. 3, on page 140. Thus one of ordinary skill in the art could reasonably have expected to increase the efficiency of transfection of the complexes of Birnstiel. It would have been similarly obvious to use the resulting compositions to deliver the nucleic acid of Wu intravenously as taught by Wu, because Wu teaches that asialoglycoprotein-targeted nucleic acid particles should be delivered in vivo. In view of the results of Wu, one would have a reasonable expectation of success for in vivo delivery of these particles.

Response to Arguments

Applicant's arguments filed 8/26/03 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant argues at pages 14 and 15 of the response that it would not have been obvious to substitute protamine sulfate for polylysine because Birnstiel teaches that such a substitution results in about 10-fold lower transfection efficiency. This is unpersuasive because the rejection set forth above relies on an embodiment of Birnstiel in which free protamine sulfate is added to existing polylysine/transferrin/DNA complexes, resulting in an improvement over the optimal polylysine/transferrin/DNA complexes in the absence of free protamine sulfate. Note that Birnstiel states that for each polylysine or protamine added, a transfection efficiency was obtained at least equivalent to that obtained when using the optimum amount of conjugate in the absence of free polycation salt. Also note that in every concentration tested, addition of free protamine sulfate provides better transfection efficiency than does addition of a free poly-L-lysine. See Table 1 at column 27. It follows that if every polylysine added yielded at least equivalent results to the optimum amount of conjugate in the absence of free polycation salt, then the addition of protamine sulfate must have resulted in an improvement over that optimum. For this reason Applicant's arguments of unexpected results wherein protamine sulfate provided greater transfection efficiency than polylysine (applied in the response to the rejections under 35 USC 103), would not be persuasive if applied to this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 77, 89, 93, 94, 98-100, 104, 107-109, 139-141, 144-146, 156, 164, 168, 169, and 172-177 are rejected under 35 U.S.C. 102(b) as being anticipated by Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992).

Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine, plasmid DNA, and cationic lipids, and methods of using the complexes to transfect liver cells (see abstract). The complexes have a net positive charge (see page 139, column 2, third full paragraph. Absent evidence to the contrary, the positive charge is on the surface of the particles, as required by claim 79. Association of positively charged polylysine/DNA complexes with cationic lipids should reasonably result in binding of the hydrophobic portion of the lipids with the hydrophobic portions of the polylysine/DNA complex, and sequestration of these portions away from the hydrophilic medium, resulting in a positively charged surface. The ratio of nucleic acid:lipid:polycation is 1 microgram : 103 nmol : 3 microgram, assuming a molecular weight of 807 D for the cationic lipid DOGS, and use of 8.3 micrograms of DOGS. See Fig. 2 on page 140. This ratio is in the range of ratios required by claims 93 and 99. The mean diameter size of the complexes ranges from about 280 to 560 nanometers (see Fig. 4 on page 140), meeting the limitations of claim 94.

Thus Mack anticipates the claims.

Response to Arguments

Applicant's arguments filed 8/26/03 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant acknowledges that the cited art teaches polycationic polypeptides, but argues that it does not teach salts of the polycationic polypeptides. This is unpersuasive for the following reasons. Mack teaches that polylysine of MW=39,400 was purchased from Sigma. See sentence bridging pages 138 and 139. As evidenced by page 1745 of the 1992 Sigma Chemical Company catalog, Sigma offers poly-L-lysine in this molecular weight range only as hydrobromide or hydrochloride salts. Absent evidence to the contrary, the polylysines of '587 and Mack are salts, and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 77, 91, 98, 104, 107-109, 139-141, 144-146, 156, 166 and 172-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Am. J. Med.

Sci. 307(2): 138-143, 1992) in view of Curiel et al (US Patent 5,521,291, issued 5/28/96).

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine salt/gene complexes improves transfection efficiency. See abstract and page 138, column 2, lines 1-4 and 18-22. In particular Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine salt, plasmid DNA, and cationic lipids, and methods of using the complexes to transfect liver cells (see abstract). The complexes have a net positive charge (see page 139, column 2, third full paragraph). Association of positively charged polylysine/DNA complexes with cationic lipids should reasonably result in binding of the hydrophobic portion of the lipids with the hydrophobic portions of the polylysine/DNA complex, and sequestration of these portions away from the hydrophilic medium, resulting in a positively charged surface. The ratio of nucleic acid:lipid:polycation is 1 microgram : 103 nmol : 3 microgram, assuming a molecular weight of 807 D for the cationic lipid DOGS, and use of 8.3 micrograms of DOGS. See Fig. 2 on page 140. The mean diameter size of the complexes ranges from about 280 to 560 nanometers (see Fig. 4 on page 140).

Mack does not teach modified lipids, polycations, insulin, LDL, or antibodies as a targeting ligand, nor does Mack teach polylysine having 20-100 residues.

Curiel teaches conjugates of polylysine and targeting ligands. The polylysine may have from 20-1000 residues, and states that the length of the polylysine is selected by routine experimentation. See column 15, lines 1-13. The targeting ligand may be an asialoglycoprotein such as asialotransferrin, or it may be LDL, HIV gp120, TNF, insulin, or an antibody. See column 10, lines 25-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polylysine in the range of 20-100 residues in the invention of Mack

because Curiel teaches that the length of polylysine in a targeting conjugate may be in this range and that the specific length is arrived at by routine experimentation. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute any desired targeting ligand for asialoglycoprotein. One would have been motivated to do so because Curiel teaches that a variety of targeting ligands including asialoglycoproteins, lipoproteins, insulin, and antibodies may be used in an exchangeable fashion depending on the desired target cell.

Claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988) in view of Mack et al (1992).

Wu teaches a method of intravenously delivering to cells *in vivo* DNA encoding a reporter gene (chloramphenicol acetyltransferase). Wu teaches the formation of complexes between the DNA and asialoglycoprotein-modified polylysine. See abstract.

Wu does not teach the addition of lipids to the complex.

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine salt/gene complexes improves transfection efficiency. See abstract and page 138, column 2, lines 1-4 and 18-22. In particular Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine, plasmid DNA, and cationic lipids, and methods of using the complexes to transfect liver cells (see abstract). The complexes have a net positive charge (see page 139, column 2, third full paragraph). Association of positively charged polylysine/DNA complexes with cationic lipids should reasonably result in binding of the hydrophobic portion of the lipids with the hydrophobic portions of the polylysine/DNA complex, and sequestration of these

portions away from the hydrophilic medium, resulting in a positively charged surface. The ratio of nucleic acid:lipid:polycation is 1 microgram : 103 nmol : 3 microgram, assuming a molecular weight of 807 D for the cationic lipid DOGS, and use of 8.3 micrograms of DOGS. See Fig. 2 on page 140. This ratio is in the range of ratios required by claims 93 and 99. The mean diameter size of the complexes ranges from about 280 to 560 nanometers (see Fig. 4 on page 140).

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the nucleic acids of Wu according to the procedure of Mack because Mack teaches that addition of DOGS improves transfection efficiency.

Thus the invention as a whole was *prima facie* obvious.

Claims 113, 128, 131, 136, and 147-153 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988) and Mack et al (1992) as applied to claims 77, 89, 93, 84, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177 above, and further in view of Curiel et al (US Patent 5,521,291, issued 5/28/96).

Wu and Mack can be combined to render obvious methods of delivering to cells *in vivo* nucleic acids encoding a reporter gene by contacting the cells with complexes comprising a targeting ligand-modified polycationic polypeptide salt, the nucleic acid, and the cationic lipid DOGS.

These references do not teach modified lipids, polycations, insulin, LDL, or antibodies as a targeting ligand.

Curiel teaches conjugates of polylysine and targeting ligands. The polylysine may have from 20-1000 residues, and states that the length of the polylysine is selected by routine experimentation. See column 15, lines 1-13. The targeting ligand may be an

asialoglycoprotein such as asialotransferrin, or it may be LDL, HIV gp120, TNF, insulin, or an antibody. See column 10, lines 25-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polylysine in the range of 20-100 residues because Curiel teaches that the length of polylysine in a targeting conjugate may be in this range and that the specific length is arrived at by routine experimentation. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute any desired targeting ligand for asialoglycoprotein. One would have been motivated to do so because Curiel teaches that a variety of targeting ligands including asialoglycoproteins, lipoproteins, insulin, and antibodies may be used in an exchangeable fashion depending on the desired target cell.

Claims 77, 88, 89, 93, 94, 98-100, 104, 105, 113, 115-117, 125, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 159, 163, 164, 168, 169, and 172-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung et al (US Patent 5,651,964, issued 7/29/97), in view of Trubetskoy et al (1992), Mack (1992), and Kern et al (CANCER RESEARCH, (1990 Aug 15) 50 (16) 5184-7).

Hung teaches methods of suppressing growth of a neu-oncogene-mediated tumor in a mammal by delivery to the tumor of a plasmid comprising a nucleic acid sequence encoding an adenoviral E1A gene product. See claim 2.

Hung does not teach a composition comprising a polycationic polypeptide salt, a nucleic acid, a lipid, or a targeting moiety.

Trubetskoy teaches of antibody-modified polylysine, plasmid DNA, and cationic liposomes, and methods of using the complexes to transfect mouse lung endothelial cells (see abstract).

Mack teaches that addition of cationic lipids to targeted polylysine salt/gene complexes improves transfection efficiency above that obtained in the absence of lipids and/or polycations. See Fig. 2 at page 140.

Kern teaches that neu is overexpressed in several types of lung cancer. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Hung by complexing the E1A-encoding plasmid with the targeted polycationic polypeptide of Trubetskoy and the lipids of Mack for delivery to mouse lung cells in vivo. One would have been motivated to do so because Mack teaches that addition of targeted polycations and cationic lipids to plasmid DNA improves transfection efficiency. One would have been motivated to deliver the complexes to a lung tumor because Kern teaches that many lung tumors are characterized by overexpression of neu. One would have had a reasonable expectation of success because the targeting ligand of Trubetskoy mediated successful transfection of mouse lung cells in vitro. Further, if one followed the teachings of Mack in assembling the delivery complex, one would have obtained a complex of less than 400 nm, as taught by Mack (see Fig. 4 on page 140).

Claims 90, 92, 101, 106, 127, 129, 165, 167, and 168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu and Mack as applied to claims 77, 89, 93, 84, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177 above and further in view of Trubetskoy et al (1992), and Harris et al (US Patent 5,650,096, issued 7/22/97).

Wu and Mack can be combined to render obvious methods of delivering to cells in vivo nucleic acids encoding a reporter gene by contacting the cells with complexes

comprising a targeting ligand-modified polycationic polypeptide salt, the nucleic acid, and the cationic lipid DOGS.

These references do not teach compositions comprising the cationic lipid DC-Chol, or a neutral colipid.

Trubetskoy teaches complexes of a targeting antibody-modified polycationic polypeptide salt, plasmid DNA, the cationic lipid DC-Chol and the neutral lipid DOPE. See Abstract and paragraph bridging pages 311 and 312.

Harris teaches that the cationic lipids DC-Chol and DOGS are both cationic amphiphiles useful for the delivery of nucleic acids. See column 4, lines 19-29.

MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, the utility of DC-Chol and DOGS, in DNA delivery complexes was well known in the prior art, so it would have been obvious to substitute DC-Chol for DOGS. It would have been further obvious to include a neutral colipid as taught by Trubetskoy, particularly because it was well known in the art that neutral colipids should be included with cationic lipids to facilitate delivery to cells of DNA. See e.g. Harris column 3, lines 14-19.

Thus the invention as a whole was prima facie obvious.

Claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154, 155, 170, and 171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu and Mack as applied to claims 77, 89, 93, 84, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177, and further in view of Torchilin et al (FASEB J. 6(9): 2716-2719, 1992).

Wu and Mack can be combined to render obvious a method of intravenously delivering to cells DNA encoding a reporter gene (chloramphenicol acetyltransferase), wherein the DNA is complexes with a ligand-modified polycationic polypeptide salt and a lipid. These references do not teach shielding of the complex, or modification with polyethylene glycol (PEG).

Torchilin teaches that PEG-modification of targeted liposomes is advantageous for intravenous delivery because it allows prolonged circulation and avoidance of rapid clearance. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to shield the composition of Wu and Mack by attachment of polyethylene glycol. One would have been motivated to do so because Torchilin teaches that this overcomes the problem of rapid particle clearance from the bloodstream, thereby increasing the chance of accurate targeting.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 8/26/03 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant addresses the forgoing obviousness rejections at pages 23-25 of the response. Applicant acknowledges that the cited art teaches polycationic polypeptides,

but argues that it does not teach salts of the polycationic polypeptides. This is unpersuasive for the following reasons. Mack teaches that polylysine of MW=39,400 was purchased from Sigma. See sentence bridging pages 138 and 139. As evidenced by page 1745 of the 1992 Sigma Chemical Company catalog, Sigma offers poly-L-lysine in this molecular weight range only as hydrobromide or hydrochloride salts. Absent evidence to the contrary, the polylysines of '587 and Mack are salts.

Applicant also argues that none of the cited references teaches "complexes with the physical characteristics (e.g. size etc.)" taught in the instant specification. This is unpersuasive because Mack teaches complexes of the required size and other physical characteristics of the invention as claimed, as stated in the rejection. Applicant further argues that the instant specification provides unexpectedly high transfection efficiency relative to the prior art. Applicant relies for support on page 23, lines 10-18, page 43, lines 9-15 and 26-28, and Examples 10 and 14. Pages 23 and 43 provide no such support, and no page of the specification has 28 lines of text. Perhaps Applicant intended page 45, lines 7-15. These passages relate specifically to the use of protamine sulfate to increase transfection efficiency beyond that obtained by use of polylysine, and characterize this result as unexpected in view of the prior art. Applicant's arguments are unpersuasive with respect to forgoing rejections because none of the rejected claims limits the identity of the polycationic polypeptide salt to protamine sulfate, and no evidence of unexpected results for any other polycationic polypeptide salt is presented. While an obviousness rejection may be overcome by presentation of evidence of unexpected results, Applicant is reminded that the evidence

must be reasonably commensurate in scope with the claimed invention. See, MPEP 2144.08B and *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). In this case, Applicant has presented no evidence that any polylysine salt composition gave better transfection efficiency than those in the prior art, e.g. those of Mack. Applicant has not addressed the alternative explanation that the alleged unexpected improvement seen with protamine sulfate is not due to the amino acid sequence of the protamine sulfate, rather than to its salt characteristics. Furthermore, as discussed below after the next set of obviousness rejections, the prior art taught that protamine sulfate could enhance transfection efficiency beyond that obtained with polylysine, so Applicants' assertion that such a result was unexpected is untenable. See Birnstiel et al, below.

Claims 77, 80, 81, 83-86, 98, 103, 110-112, and 156-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992) in view of Birnstiel et al (US Patent 5,922,859, issued 7/13/99).

Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine, plasmid DNA, and cationic lipids, and methods of using the complexes to transfect liver cells (see abstract). The complexes have a net positive charge (see page 139, column 2, third full paragraph). Absent evidence to the contrary, the positive charge is on the surface of the particles. Association of positively charged polylysine/DNA complexes with cationic lipids should reasonably result in binding of the hydrophobic portion of the lipids with the hydrophobic portions of the polylysine/DNA complex, and sequestration of these portions away from the hydrophilic medium,

resulting in a positively charged surface. The ratio of nucleic acid:lipid:polycation is 1 microgram : 103 nmol : 3 microgram, assuming a molecular weight of 807 D for the cationic lipid DOGS, and use of 8.3 micrograms of DOGS. See Fig. 2 on page 140. The mean diameter size of the complexes ranges from about 280 to 560 nanometers (see Fig. 4 on page 140).

Mack does not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor does Mack teach a sulfate salt, or protamine as a polycation.

Birnstiel teaches methods and compositions for delivering DNA to cells. The complexes comprise a polycationic polypeptide for condensing the DNA, as well as a targeting ligand. See e.g. claims 1, 14, and 17. Birnstiel also teaches that protamine and polylysine salts may be used interchangeably in such compositions. See column 18 line 66 to column 19, line 25. As evidenced by the instant specification at page 47 (Table 5) protamine sulfate meets the limitations of claim 81 with respect to the quantities of arginine and lysine required in the polypeptide salt.

Birnstiel teaches compositions for delivering nucleic acids to cells. The compositions comprise

- (a) the nucleic acid to be transferred;
 - (b) an internalizing factor-bonding factor conjugate complexed to the nucleic acid to be transferred; and
 - (c) a non-covalently bound substance having an affinity for nucleic acid, which substance is not a component of said internalizing factor-bonding factor conjugate; wherein
- (i) said internalizing factor is cell type specific for said eukaryotic cells;

- (ii) said non-covalently bound substance is selected from a group consisting of polycations that are capable of condensing the nucleic acid to be transferred, histones, and HMGI; and
- (iii) the ability of said complex to internalize and/or achieve expression of said nucleic acid to be transferred is increased compared to the complex containing only the nucleic acid to be transferred and the internalizing factor-bonding factor conjugate.

Birnstiel exemplifies polylysine/transferrin conjugates as "internalizing factor-bonding factor conjugates", but teaches that the internalizing factor may be an asialoglycoprotein such as asialotransferrin, or it may be LDL, HIV gp120, TNF, insulin, or an antibody. See column 7, lines 39-49. Birnstiel exemplifies a variety of polycationic polypeptide salts as "a non-covalently bound substance having an affinity for nucleic acid." Experiments characterizing these compositions were conducted. First Birnstiel studied compositions comprising only transferrin/polylysine conjugates complexed with DNA, and determined the optimum amount of conjugate per unit DNA. Then Birnstiel formed complexes between DNA and a suboptimal amount of transferrins/polylysine conjugate, and then added free polycationic polypeptide salts such as polylysine (55, 90, or 450 residues), protamine sulfate, or histone. Birnstiel found that "the addition of polylysines and natural protamine and the histones investigated achieved a DNA import efficiency at least equivalent to that obtained when using the conjugates which had been found to be optimum." See column 17, line 10 to column 19, line 25, especially column 18, line 47 to column 19, line 25, and Table 1 at column 27.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lipids of Mack to the compositions of Birnstiel because Mack

teaches that the addition of cationic lipids to polycation/ligand/DNA complexes increases transfection efficiency more than 10-fold over that achieved in the absence of lipids, without the need for chloroquine. See paragraph bridging columns 1 and 2, and Fig. 3, on page 140. Thus one of ordinary skill in the art could reasonably have expected to increase the efficiency of transfection of the complexes of Birnstiel by adding the lipids as taught by Mack.

Claims 106 and 118-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992) and Wu et al (J. Biol. Chem. 263(29): 14621-14624, 1988), as applied to claims 77, 89, 93, 84, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177, and further in view of Birnstiel et al (US Patent 5,922,859, issued 7/13/99).

Wu and Mack can be combined to render obvious a method of intravenously delivering to cells DNA encoding a reporter gene (chloramphenicol acetyltransferase), wherein the DNA is complexes with a ligand-modified polycationic polypeptide and a lipid. These references do not teach shielding of the complex, or modification with polyethylene glycol (PEG).

These references do not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor do they teach a sulfate salt, or protamine as a polycation.

The teachings of Birnstiel are discussed above. Birnstiel teaches polylysine/transferrin/nucleic acid complexes comprising protamine sulfate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lipids of Mack to the compositions of Birnstiel because Mack teaches that the addition of cationic lipids to polycation/ligand/DNA complexes increases transfection efficiency more than 10-fold over that achieved in the absence of lipids, without the need for chloroquine. See paragraph bridging columns 1 and 2, and Fig. 3, on page 140. Thus one of ordinary skill in the art could reasonably have expected to increase the efficiency of transfection of the complexes of Birnstiel. It would have been similarly obvious to use the resulting compositions to deliver the nucleic acid of Wu intravenously as taught by Wu, because Wu teaches that asialoglycoprotein-targeted nucleic acid particles should be delivered in vivo. In view of the results of Wu, one would have a reasonable expectation of success for in vivo delivery of these particles.

Response to Arguments

Applicant's arguments filed 8/26/03 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant argues at pages 14, 15 and 22 of the response that it would not have been obvious to substitute protamine sulfate for polylysine because Birnstiel teaches that such a substitution results in about 10-fold lower transfection efficiency. This is unpersuasive because the rejection set forth above which relies on an embodiment of Birnstiel in which free protamine sulfate is added to existing polylysine/transferrin/DNA complexes, resulting in an improvement over the optimal polylysine/transferrin/DNA

complexes in the absence of free protamine sulfate. Note that Birnstiel states that for each polylysine or protamine added, a transfection efficiency was obtained at least equivalent to that obtained when using the optimum amount of conjugate in the absence of free polycation salt. Also note that in every concentration tested, addition of free protamine sulfate provides better transfection efficiency than does addition of a free poly-L-lysine. See Table 1 at column 27. It follows that if every type of polylysine added yielded at least equivalent efficiency to that obtained with the optimum amount of conjugate in the absence of free polycation salt, then the addition of protamine sulfate must have resulted in an improvement over that optimum. For this reason Applicant's arguments of unexpected results wherein protamine sulfate provided greater transfection efficiency than polylysine are not persuasive, and the rejection is deemed proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-

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272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.



DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.